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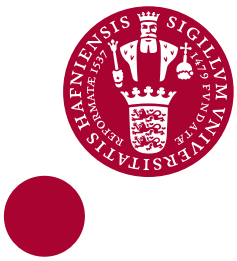

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Study designs may influence results: the problems with questionnaire-based case–control studies on the epidemiology of glioma

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Glioma is a rare brain tumour with a very poor prognosis and the search for modifiable factors is intense. We reviewed the literature concerning risk factors for glioma obtained in case–control designed epidemiological studies in order to discuss the influence of this methodology on the observed results. When reviewing the association between three exposures, medical radiation, exogenous hormone use and allergy, we critically appraised the evidence from both case–control and cohort studies. For medical radiation and hormone replacement therapy (HRT), questionnaire-based case–control studies appeared to show an inverse association, whereas nested case–control and cohort studies showed no association. For allergies, the inverse association was observed irrespective of study design. We recommend that the questionnaire-based case–control design be placed lower in the hierarchy of studies for establishing cause-and-effect for diseases such as glioma. We suggest that a state-of-the-art case–control study should, as a minimum, be accompanied by extensive validation of the exposure assessment methods and the representativeness of the study sample with regard to the exposures of interest. Otherwise, such studies cannot be regarded as 'hypothesis testing' but only 'hypothesis generating'. We consider that this holds true for all questionnaire-based case–control studies on cancer and other chronic diseases, although perhaps not to the same extent for each exposure–outcome combination.

Studies of the aetiology of glioma, the commonest malignant brain tumour, with a very poor prognosis, are urgently needed, specifically to identify modifiable risk factors. The main reason that researchers have used the case–control design as the model of choice for epidemiological studies on the causes of glioma is that it a rare cancer, with an incidence of 4 per 100 000 people (World Standard Population) in Denmark, an incidence typical for a high-income country (Christensen *et al*, 2003). Furthermore, the design limits the time required to obtain data, the cost is lower than that of more time-consuming designs and a wide range of suspected risk factors can be examined in the same study. In case–control studies, questionnaire data, blood samples and tissue specimens can be obtained from both cases and controls, thereby allowing analysis of both environmental and genetic factors and their interactions.

In questionnaire-based case–control studies, it is anticipated that cases can recall past events with sufficient accuracy. This *a priori* assumption is somewhat naive in the case of glioma in view of the well-known clinical presentation of the disease. The cancer itself, surgery, radiotherapy, chemotherapy and any combination of treatment may strongly influence the overall cognitive capacity of patients. Some have overt cognitive deficits and may therefore be unable to remember past events or have selective recall. Researchers may have to interview a proxy of the patient, as is often the case in case–control studies of risk factors for glioma.

Finding suitable controls presents another challenge. They must be from the same study population as the cases, as the source may influence reported exposures, and selection may be introduced when potential controls decide whether to participate in a study. If these sources of error are systematically different in terms of the

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Table 1. Overview of reports by study design on three potential risk factors for glioma: medical radiation, exogenous hormone use and allergic disease

First author, country, year, study design	Case–control study *N* glioma cases/*N* controls; % proxy in case group; % control participation Cohort study *N* participants; *N* glioma cases; mean follow-up	Definition of exposure and risk estimates
Medical radiation		
Preston-Martin, USA, 1989, case–control	202/202 (Male) Not provided Not provided	Full-mouth X-ray < 25 years age: every 2–5 years, OR, 1.6 (0.7–3.6); once a year, OR, 3.0 (0.6–14.9); *P*-value for trend 0.04
Neuberger, USA, 1991, case–control	7/14 100% (Cases and controls deceased) 100%	Dental X-rays, OR, 10.66 (1.95–58.25)
Schlehofer, Germany, 1992, case–control	115/418 <1% 72%	Any X-rays of head and neck OR, 1.21 (0.6–2.3)
Ryan, Australia, 1992, case–control	110/419 Not provided 63%	Ever dental X-rays, OR, 0.42 (0.24–0.76) Full-mouth X-rays, OR, 1.98 (0.72–5.39)
Zampieri, Italy, 1994, case–control	195/195 (Hospital controls) 100% 100%	Any diagnostic Xx-ray, OR, 0.4 (0.1–1.0)
Ruder, USA, 2006, case–control	798/1175 Not provided 70% of 1670 eligible	Ever full-mouth dental X-rays, OR 0. 75, (0.61–0.92)
Blettner, Germany, 2007, case–control	366/732 11% 63% (80% for cases)	Any medical ionising radiation, OR, 0.62 (0.47–0.82)
Davis, USA, 2011, case–control	205/333 Not provided Not provided	1 or more yearly dental X-rays, OR, 0.60 (0.21–1.73) 3 or more full-mouth X-ray, OR, 0.70 (0.40–1.21)
Exogenous hormones		
Huang, USA, 2004, case–control	341/527 43% 72%	Ever OC, OR, 0.83 (0.58–1.20) Ever HRT, OR, 0.73 (0.49–1.10)
Hatch, USA, 2005, case–control	212/436 Hospital controls 16% 89%	Ever OC, OR, 0.66 (0.44–1.00) Ever HRT, OR, 0.66 (0.41–1.09)
Wigertz, Sweden, 2006, Case–Control	132/323 Proxies excluded Not provided	Ever OC, OR, 0.8 (0.5–1.4) Ever HRT, OR, 0.9 (0.4–1.7)
Silvera, Canada, 2006, cohort	89,835 Women 120 Cases of glioma Mean follow-up 16.4 years	Ever OC, RR, 1.01 (0.68–1.52) Ever HRT, RR, 0.92 (0.55–1.56)
Benson, UK, 2008, cohort	1 249 670 Women 646 Glioma cases Mean follow-up 6.3 years	OC <5 years, RR, 0.88 (0.72–1.09) OC >5 years, RR, 0.88 (0.72–1.06)
Felini, USA, 2009, case–control	619/650 79% 37%	Ever OC, OR, 0.62 (0.47–0.82) Ever HRT, OR, 0.57 (0.41–0.79)
Michaud, Europe, 2010, cohort	276 212 Women 193 Glioma cases Mean follow-up 8.4 years	Former OC, RR, 0.84 (0.61–1.18) Current OC, RR, 1.23 (0.53–2.83) Former HRT, RR, 0.93 (0.55–1.56) Current HRT, RR, 0.76 (0.49–1.19)
Kabat, USA, 2011, cohort	3 Twin cohorts I: *N* = 14 535 37 Glioma cases Median follow-up 26 years II: *N* = 29 573 42 glioma cases Median follow-up 26 years Combination of I–II *N* = 52 067 68 Glioma cases Median follow-up 20 years	Ever HRT, HR, 0.99 (0.63–1.56)

Table 1. (Continued)

First author, country, year, study design	Case–control study *N* glioma cases/*N* controls; % proxy in case group; % control participation Cohort study *N* participants; *N* glioma cases; mean follow-up	Definition of exposure and risk estimates
Andersen, Denmark, 2013, case–control	411/2587 0% (Nested in cohort) 100% (Nested in cohort)	Ever HRT, 0.9 (0.8–1.1)
Anic, USA, 2014, case–control	507/141 Friend controls/554 community controls 2.6% Not provided	Ever OC, OR, 0.77 (0.57–1.03)
Benson, UK, 2015, case–control	689/13,997 Not provided Not provided	Ever (1 + prescription) HRT, 1.14 (0.93–1.40)
Allergy		
Cicuttini, Australia, 1997, case–control	416/422 44% 65%	Asthma: 0.8 (0.5–1.2) Eczema: 0.9 (0.5–1.4)
Schlehofer, Australia, Canada, France, Germany, Sweden, 1999, case–control	1178/1987 26% Not provided	Any allergy, OR, 0.59 (0.49–0.71)
Wiemels, USA, 2002, case–control	405/402 34% 74%	Any allergy, OR, 0.47 (0.33–0.67) Excluding proxy cases, OR 0.65 (0.43–0.97)
Brenner, USA, 2002, case–control	489/799 hospital controls 24% 86%	Any allergy, OR, 0.67 (0.52–0.86)
Schwartzbaum, Sweden, 2003, cohort	3 Twin cohorts I: $N = 14\,535$ 37 Glioma cases Median follow-up 26 years II: $N = 29\,573$ 42 Glioma cases Median follow-up 26 years Combination of I–II $N = 52\,067$ 68 Glioma cases Median follow-up 20 years	Any allergy, self-report Cohort I: HR, 0.45 (0.19–1.07) Cohort II: HR, 1.09 (0.48–2.48) Discharge with immune-related diseases (asthma, croup, eczema, psoriasis and autoimmune disease) Cohort I + II: HR, 0.46 (0.14–1.48)
Wiemels, USA, 2004, case–control	226/289 Not provided Not provided	Serum IgE level elevated, OR, 0.37 (0.22–0.64) Self-reported allergies 1–3 Allergies, OR 0.69 (0.42–1.1) 4 + Allergies, OR, 0.50 (0.28–0.88)
Schoemaker, UK, 2006, case–control	965/1716 Not provided 45%	Any allergy, OR, 0.63 (0.53–0.76)
Wigertz, Denmark, Norway, Finland, Sweden, UK, 2007, case–control	1527/3309 13% 50%	Any allergy, OR, 0.70 (0.61–0.80)
Scheurer, USA, 2008, case–control	325/600 4% 53%	Allergy or asthma, OR, 0.34 (0.23–0.51) Antihistamines, OR, 1.37 (0.87–2.14) Among allergic persons, antihistamine use OR, 2.54 (1.28–5.03)
Il'yasova, USA, 2009, case–control	388/(80 Siblings/191 friends/177 clinic based) Not provided 83%	Any allergy (sibling controls) OR, 0.53 (0.15–1.84) (friend controls) OR, 0.54 (0.28–1.07) (Clinic-based controls) OR, 0.34 (0.23–0.50)
Berg-Beckhoff, Germany, 2009, case–control	366/1535 3.2% 63%	Any allergy, OR, 0.92 (0.70–1.22)
Wiemels, USA, 2009, case–control	535/565 24% 92%	Any allergy, OR, 0.50 (0.36–0.70)
McCarthy, US, 2011, case–control	419/612 (Hospital controls) Not provided 71%	Any allergy, OR, 0.60 (0.46–0.79) Any antihistamine use, OR, 0.76 (0.59–0.99)

Table 1. (Continued)

First author, country, year, study design	Case–control study *N* glioma cases/*N* controls; % proxy in case group; % control participation Cohort study *N* participants; *N* glioma cases; mean follow-up	Definition of exposure and risk estimates
Schlehofer, Europe, 2011, case–control	275/528 0% (Nested in cohort) 100% (Nested in cohort)	Serum IgE positive, OR, 0.73 (0.51–1.06) *P* for trend of positivity, 0.11
Calboli, USA, 2011, case–control	169/520 0% (Nested in cohort) 100% (Nested in cohort)	Serum IgE above normal, OR, 0.72 (0.51–1.03)
Turner, Australia, Canada, France, Israel, New Zealand, 2013, case–control	793/2374 17% Not provided	Any allergy, OR, 0.73 (0.60–0.88)
Cahoon, USA, 2014, cohort	4 501 578 Mio men, 4383 Glioma cases Mean follow-up 11.7 years	Any allergy Latency >2 years, HR, 0.85 (0.72–1.01) Latency>10 years, HR, 0.6 (0.4–0.8) *P* for trend of latency, 0.02

Abbreviations: HR = hazard ratio; HRT = hormone replacement therapy; OC = oral contraception; OR = odds ratio; RR = relative risk.

exposures of interest from those in the case group, bias will be present. Bias can be addressed partly with statistical tools; however, they require either some idea of the nature and magnitude of bias from validation studies or assumptions about potential bias in sensitivity analyses. Neither necessarily leads to a satisfactory outcome, especially if the results differ substantially according to the assumptions. Despite these potentially serious limitations of case–control studies, there has been no in-depth debate about situations in which questionnaire-based case–control studies are unlikely to provide reliable results. In some narrative syntheses and meta-analytical reviews, the results of such studies contribute equally to the evidence base, even though application of study quality indicators is recommended when summarising evidence. It is therefore important to consider the level of evidence from case–control studies based solely on differential reconstruction of past exposures as compared with that from prospective studies for investigating glioma, when reconstruction of exposure is hampered by the outcome itself.

In this review, we critically appraise the evidence from both case–control and cohort studies of three risk factors for glioma in humans: medical radiation, exogenous hormone use and allergy. The objective is to provide some insight into the difficulty associated with choosing a study design when studying the risk factors for glioma. We also propose considerations for applying scientific weight to the results of case–control studies in this context.

We searched the Medline–PubMed database on 18 November 2015 using the following search strategy:

Search ((‘Glioma/epidemiology’[Majr] OR (glioma AND epidemiology))) AND ((((‘Risk Factors’[Mesh]) OR ‘Environment and Public Health’[Mesh])) OR (Risk OR exposure OR factor* OR cause*)) Filters: Humans; Meta-Analysis; Review; Systematic Reviews

OR

Search ((((((‘Glioma/epidemiology’[Majr] OR (glioma AND epidemiology))) AND ((((‘Risk Factors’[Mesh]) OR ‘Environment and Public Health’[Mesh])) OR (Risk OR exposure OR factor* OR cause*))) AND Humans[Mesh])) AND ((((‘Case-Control Studies’[Mesh]) OR ‘Cohort Studies’[Mesh]) AND Humans[Mesh]) Filters: Humans

This search provided 3018 hits. Using the inclusion criteria English language paper, adult glioma, case–control study or cohort study and excluding reviews and/or meta-analyses, overview or commentary, qualitative methodology, children and adolescents, genetic exposures and mortality or survival as the outcome, we identified reports of original studies that included the three selected risk factors for glioma. Our search was intended to be neither comprehensive nor systematic for this review. We are aware that we did not identify some studies, such as those in which the word ‘glioma’ was not in the title, abstract or keywords and those in which none of the three risk factors was mentioned in the title or abstract.

From the selected papers, we extracted the characteristics of the study. We then compared the evidence from studies based on recall by cases and controls with that from studies with either a case–control design, with objective (recall-independent) assessment of exposure or a prospective cohort design.

We selected 30 case–control studies and six cohort studies on the association between glioma and medical radiation (Preston-Martin *et al*, 1989; Neuberger *et al*, 1991; Schlehofer *et al*, 1992; Ryan *et al*, 1992; Zampieri *et al*, 1994; Ruder *et al*, 2006; Blettner *et al*, 2007; Davis *et al*, 2011), exogenous hormone use (Huang *et al*, 2004; Hatch *et al*, 2005; Wigertz *et al*, 2006; Silvera *et al*, 2006; Benson *et al*, 2008, 2015; Felini *et al*, 2009; Michaud *et al*, 2010; Kabat *et al*, 2011; Andersen *et al*, 2013; Anic *et al*, 2014; 2015) or allergic diseases (Cicuttini *et al*, 1997; Schlehofer *et al*, 1999, 2011; Wiemels *et al*, 2002, 2004, 2009; Brenner *et al*, 2002; Schwartzbaum *et al*, 2003; Schoemaker *et al*, 2006; Wigertz *et al*, 2007; Scheurer *et al*, 2008; Berg-Beckhoff *et al*, 2009; Il’yasova *et al*, 2009; 2009; McCarthy *et al*, 2011; Calboli *et al*, 2011; Turner *et al*, 2013; Cahoon *et al*, 2014). Table 1 lists the key characteristics of the selected studies.

MEDICAL RADIATION: INFORMATION FROM PARTICIPANTS ONLY

Ionising radiation is a long-established human carcinogen. Early cohort studies of patients who received radiation treatment to the scalp to treat tinea capitis or skin haemangioma during childhood had an increased risk for glioma, especially after treatment at an early age (see, e.g., Ron *et al*, 1988). Early case–control studies suggested increased risks for glioma after exposure to dental X-rays or X-rays to the head and neck (Preston-Martin *et al*, 1989; Neuberger *et al*, 1991; Ryan *et al*, 1992; Schlehofer *et al*, 1992). In contrast, the German part of the Interphone study (a multinational interview-based case–control study on mobile phone use and other risk factors for brain tumours, acoustic neuroma and salivary gland tumours) indicated that exposure to any medical ionising radiation significantly reduced the risk for glioma (OR, 0.63; 95% CI, 0.48–0.83) in a study of 366 glioma

patients (of whom 11% reported information on exposure through proxies) and 1538 controls (Blettner *et al*, 2007). Other research groups have reported a similar protective effect of medical ionising radiation. In a study in Italy in 1984, of 195 cases and hospital controls, in which all information was obtained from proxies, the OR for any diagnostic X-ray was 0.4 (95% CI, 0.1–1.0; Zampieri *et al*, 1994). In two studies in the USA with 798 and 205 cases (proportions of proxies not reported), reduced ORs were found after exposure to full-mouth dental X-rays (OR, 0.75; 95% CI, 0.61–0.92; Ruder *et al*, 2006) and after one or more yearly dental X-rays or three or more full-mouth X-rays (0.60; 95% CI, 0.21–1.73 to 0.70; 95% CI, 0.40–1.21; Davis *et al*, 2011). In personal communications, we have been informed that medical radiation appears to be protective against glioma in the entire Interphone data set and that similar results were obtained in the Gliogene study. Although authors usually appropriately discuss the possibility of chance findings, residual confounding and (more importantly) recall bias, use of proxies and selection bias, data are required to estimate the magnitude and direction of the potential error; otherwise, most of the conclusions remain speculative. Most case–control studies continue to rely on self-reported information, whereas validation from records of medical radiation or dental records should be a minimal quality assurance component of studies. This may be difficult in countries where X-ray machines are available in all hospitals, big or small, and even in some general practices, so that it would be virtually impossible to review all the records for false negatives (that is, examinations not reported by study participants). It should, however, be feasible on a small sample.

EXOGENOUS HORMONES: SELF-REPORTED USE *VERSUS* PRESCRIPTION DATA

Two methods have been used to collect information on exposure in studies of the relation between use of exogenous hormones and glioma: self-reported use and prescription data. In a case–control study in the USA with 619 women with glioma and 650 controls, self-reported use of hormone replacement therapy (HRT) was associated with an OR of 0.56 (95% CI, 0.37–0.84; Felini *et al*, 2009). This result is in line with those of a number of other case–control studies of self-reported use of oral contraceptives or HRT, reported separately (Huang *et al*, 2004; Hatch *et al*, 2005; Wigertz *et al*, 2006; Anic *et al*, 2014), which did not, however, reach statistical significance. In two case–control studies nested in population-based registries, with data on prescriptions collected prospectively and independently of the study hypothesis, use of HRT did not decrease the risk for glioma, based on 689 cases (OR, 1.14; 95% CI, 0.93–1.40) and 658 cases (OR, 0.9; 95% CI, 0.8–1.1; Benson *et al*, 2015 and Andersen *et al*, 2013). These results, based on administrative sources, corroborated those of several very large prospective cohort studies with self-reported data on use of oral contraceptives or HRT obtained before diagnosis of a glioma (Silvera *et al*, 2006; Benson *et al*, 2008; Michaud *et al*, 2010; Kabat *et al*, 2011). Overall, therefore, relying on self-reported information on use of exogenous hormones obtained retrospectively resulted in systematically lower risk estimates than when exposure was measured prospectively or from prescription data, when no convincing reductions in risk were observed.

ALLERGY: SAME DIRECTION IN RISK IRRESPECTIVE OF STUDY DESIGN

The search of an immune factor that may have a role in glioma aetiology has led to studies of several different definitions of outcomes—ranging from self-reported allergic conditions or autoimmune disorders, discharge records of allergic disorders and use of serum IgE levels as a measure of a hyperactive immune system. Several case–control studies showed consistently that self-reported allergic conditions protect against glioma. For example, in the International Adult Brain Tumour Study, with 1178 glioma patients (26% of whom reported through proxies) and 2493 population controls, an OR of 0.59 (95% CI, 0.49–0.71) was found for any self-reported allergy (Schlehofer *et al*, 1999). Other case–control studies found similarly reduced ORs; these often had substantial proportions of proxy informants: 44% (Cicuttini *et al*, 1997), 24% (Wiemels *et al*, 2002), 24% (Brenner *et al*, 2002), 13% (Wigertz *et al*, 2007), 4% (Scheurer *et al*, 2008), 3% (Berg-Beckhoff *et al*, 2009), 24% (Wiemels *et al*, 2009) and 17% (Turner *et al*, 2013); others did not provide information on the proportion of proxies (Wiemels *et al*, 2004; Schoemaker *et al*, 2006; Il'yasova *et al*, 2009; McCarthy *et al*, 2011). Two Swedish cohorts who self-reported allergies had non-significantly reduced risks for glioma: OR, 0.45 (95% CI, 0.19–1.07) among twins born in 1986–1925 but a nonsignificantly increased risk (OR, 1.09; 95% CI, 0.48–2.48) among twins born in 1926–1958 (Schwartzbaum *et al*, 2003). In a combined analysis of the two twin cohorts and discharge records of immune-related diseases, including both atopic allergic diseases as well as autoimmune diseases such as diabetes, rheumatoid arthritis and so on, as the exposure measure, the risk was reduced but not significantly (HR, 0.46; 95% CI, 0.14–1.48).

The biological marker immunoglobuline E (IgE) may provide more specificity and reduce bias stemming from self-report. In a case–control study from 2004, both self-reported allergies and IgE levels were reversely associated with gliomas in 258 cases and 289 controls but, as expected, concordance between the two outcomes was not high (Wiemels *et al*, 2004). In a further study from 2009, both self-reported allergies and IgE levels were reversely associated in 535 cases and 532 controls, but analyses showed that IgE levels obtained in glioma patients were affected by treatment with telozomide, underscoring the need for prospectively collected data (Wiemels *et al*, 2009). A case–control study nested in the EPIC cohort (Schlehofer *et al*, 2011) and thus with prospectively collected data on serum IgE levels reported a statistically nonsignificant OR of 0.73 (95% CI, 0.51–1.06) based on 275 cases. Another case–control study, nested in four large cohorts in the USA with 181 cases of glioma, found an almost identical OR of 0.72 (95% CI, 0.51–1.03) for a serum IgE level above normal (Calboli *et al*, 2011). A cohort study of hospital discharge records of 4.5 million men with a mean 12-year follow-up and 4383 events of glioma showed that any allergy was associated with an HR for glioma of 0.85 (95% CI, 0.72–1.01) with a latency of >2 years and 0.6 (95% CI, 0.4–0.8) with a latency of >10 years (Cahoon *et al*, 2014). In a meta-analyses of the 14 studies in the international Gliogene case–control study, published after our literature search, with 4533 cases and 4177 controls and $<10\%$ proxies, respiratory allergy was associated with an OR of 0.72 (95% CI, 0.58–0.90; Amirian *et al*, 2016a).

Imprecisely defined exposures such as allergic disease probably affect the validity of the findings of both case–control and cohort studies. The heterogeneous description of allergy in studies, different levels of detail in self-reporting on individual allergies and use of objective measures of serum IgE levels or discharge records further complicate interpretation of the results. Nevertheless, there is no doubt that most studies of any design, type of measure and size indicate that allergy or a hyperactive immune system, through some as yet unidenfied biological mechanisms might be protective against the development of glioma.

SYNTHESIS OF THE THREE EXAMPLES

In two of our examples, medical radiation and HRT, questionnaire-based case–control studies appeared to show an inverse association, whereas nested case–control and cohort studies showed no association. For allergies, the inverse association is observed irrespective of study design. If the inverse associations

with medical radiation and HRT use are spurious, possible explanations are over-reporting by controls, under-reporting by cases or selection bias in relation to the exposure of interest. Over-reporting by controls seems unlikely, unless the time between the reference date (censoring of risk time) and the interview date is long, when controls may incorrectly remember the dates of examinations and report those occurring after censoring of the risk time, as observed in a case–control study on paediatric brain tumours in Germany (Schüz *et al*, 2001). Selection bias may have some role, as medical radiation and HRT use are more common among more affluent people, while participation as a control is often associated with higher education and income. Under-reporting is a concern. It might occur because a patient with the very serious diagnosis of a glioma might view other medical events as less important and could easily be forgotten in an interview. The last finding is curious, because, for environmental exposures, validation studies suggest over-reporting or exaggeration by cases (for instance, in studies on mobile phone use or occupational exposure), perhaps because they try to not miss reporting something they may consider relevant in terms of their cancer diagnosis. (For discussions on bias in case–control studies on brain tumours, see, for example, Vrijheid *et al*, 2006, 2009).

After 30 years of research, we still do not know much about what causes glioma or protects people from the disease. In the search for causality, many researchers who are systematically evaluating the evidence give more weight to that from cohort studies than from case–control studies (e.g., Cochrane reviews); others go as far as considering case–control studies useful only for hypothesis generating because of their retrospective nature (Mann, 2003). In many systematic reviews and meta-analyses in the peer-reviewed literature; however, there is a tendency to categorise the evidence from case–control studies with evidence derived from prospective cohort studies and to give them equal weight. In studying glioma, we consider it critical that studies based on the recall of patients with a disease that affects the brain and possibly cognition should not be given the same weight as nested case–control studies or cohort studies. In addition to the limitations inherent in questionnaire-based case–control studies on other diseases, the risk for recall bias among cases makes it difficult to draw firm conclusions. Validation studies of recall of exposures by glioma cases and by controls often show that cases recall the past differently from controls (Vrijheid *et al*, 2006, 2009). The treatment and even the symptoms that arise before treatment, due to the presence of the tumour, may influence cognitive function, underscoring these objections. In studies of glioma, the widespread acceptance of information obtained from the closest relative—a proxy—adds to the problem of the accuracy of self-reported information. Going back to our examples, would proxies really know about the dental X-rays that the patient had during childhood? Recall bias is an issue not only for the exposure of interest but also for potential confounders in analyses of the exposure–disease relationship, as inaccurately measured confounders obviate appropriate adjustment.

As we have illustrated, studies in which information on exposure is obtained from sources other than memory for both cases and controls and in which the information on outcome is from high quality sources, are more reliable, depending on the completeness and quality of the data that can be obtained.

The cohort design is not free of problems, but it is less vulnerable to methodological errors than case–control studies that rely on the memory of cases and controls. The cohort design is therefore the preferred type for observational studies. Nevertheless, because glioma is a rare event, the case–control design may be the only one possible. During critical appraisal of the evidence derived from such studies, however, quality indicators should be applied, as they should for cohort studies. These quality indicators should address the study population (sampling frame, response rates), exposure measures (ideally showing results from validations), and discussion of potential bias affecting the risk estimation.

The superiority of the cohort design and/or access to data obtained independently of the hypothesis in studies of potential risk factors for cancer have been illustrated by cohort studies of various issues, for example, that abortions increase the risk for breast cancer (Melbye *et al*, 1997) and that our minds cause cancer (Johansen, 2012). One may say that when studying i.e. low-dose radiation and rare outcomes such as gliomas with complicating problems of recall bias and lack of validation the question cannot be reduced to just choosing cohort studies over case–control studies. Cohort studies may actually not be feasible for evaluation of this exposure. One solution might instead be to extrapolate from cohort studies with greater ranges of exposure like atomic bomb survivors or people exposed to nuclear accidents. Poorly conducted studies give rise to risk, as their outcomes often contribute to public concern and may shift the focus from the relevant to the irrelevant, as for instance in the debate about cancer risks and mobile technologies.

Observational studies on the risk factors for glioma, i.e. reports from the early case–control studies conducted at the University of California at San Francisco (USA; see, e.g., Wrensch *et al*, 2000) and the University of California at Los Angeles (USA; Preston-Martin *et al*, 1989), coordinated by the US National Cancer Institute (Inskip *et al*, 2001), the first international case–control study (Schlehofer *et al*, 1999), the Interphone study (Cardis *et al*, 2007) and probably also the most recent Gliogene case–control study (Malmer *et al*, 2007), do not provide much evidence on what causes this devastating cancer. Thus, despite all the resources that went into those studies, the results did not provide striking evidence on which to base prevention. Nevertheless, as lifestyle and environmental factors were studied comprehensively, the results may suggest that not many of the usual cancer-causing suspects have an important role in glioma aetiology. This is an important finding to be acknowledged and suggests that for the identification of causes novel ideas are needed. Recent reports on genetic risk factors for glioma suggest that these factors do have a crucial role in the risk pattern (Amirian *et al*, 2016b).

The criteria for causality are the strength of the evidence, consistency across populations, specificity, temporality, dose–response and biological plausibility (Hill, 1965). The temporal criterion should always be addressed in evaluating the evidence, whereas in case–control studies, unless secondary data sources can be used, the information is collected after diagnosis of a disease, that is, the reverse sequence in temporality. Furthermore, there are major problems in self-reporting, as cases are aware of having a fatal disease and may unconsciously change their way of looking at past events. Even physical measurements should be evaluated for the representativeness of contemporary measurements of exposure during the aetiologically relevant period, which might have been decades previously.

On the basis of this review, we recommend that the case–control design be placed lower in the hierarchy of studies for establishing cause-and-effect for diseases such as glioma, which pose challenges for accurate collection of retrospective data. A state-of-the-art case–control study should as a minimum, be accompanied by extensive validation of the exposure assessment methods and the representativeness of the study sample with regard to the exposures of interest. Otherwise, such studies cannot be termed 'hypothesis testing' but only 'hypothesis generating'. We consider that this holds true for all questionnaire-based case–control studies on all cancers and chronic diseases, although perhaps not to the same extent for each exposure–outcome combination. For example, case–control studies clearly linked smoking with lung cancer in the 1950s, prenatal radiation to the fetus with childhood leukemia in the late 1950s/early 1960s, postmenopausal oestrogens with uterine endometrial cancer in the 1960s and diethylstilbestrol with vaginal adenocarcinoma in 1971. Almost all known risk factors for breast

cancer were identified in case–control studies and much of the evidence that identified smoking and types of tobacco as the cause of about 50% of bladder cancer was based on case–control studies. However, this list does not include risk factors for glioma and these earlier studies, in some cases, showed risk estimates robust to such a degree that even potential bias could not hamper the associations observed.

We hope that the examples we have provided underscore our points and that our recommendation will be taken into account in ranking the evidence obtained from case–control studies and also in the design of such studies in cancer epidemiology.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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